A Phase I, open-label, dose escalation study of oral LGK974 in patients malignancies dependent on Wnt ligands

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Primair:Determine the MTD and/or recommended dose for expansion (RDE) of LGK974 as a single agent andin combination with PDR001 when administered to adult patients with malignancies dependent on Wntligands as specified in the inclusion...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55368

Source
ToetsingOnline

Brief title
CLGK974X2101

Condition

- Other condition
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
B-RAF mutant colorectal cancer, melanoom (skin cancer), tumors of any histological origin with documented genetic alterations upstream in the Wnt signaling pathway

Health condition

B-RAF gemuteerde colerectaal carcinoma, bepaalde vorm van borstkanker (TNBC, triple negative breastcancer), HNSCC (hoofd en hals pleiveselcelcarcinoom) en melanoom

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: anti PD-1 antibody, LGK974, melanoma, PDR001, Wnt

Outcome measures

Primary outcome

Incidence rate of dose limiting toxicities (DLTs) during the first cycle of

LGK974 and during the first 2 cycles of LGK974 in combination with PDR001.

Secondary outcome

- Safety: Frequency and severity of (serious) adverse events. Changes in

laboratory values, assessments of physical examinations, vital signs and

electrocardiograms.

- Pharmacokinetics: PK parameters.

- Pharmacodynamics: Post-treatment change from baseline in certain biomarkers.

Correlation between plasma exposure parameters of LGK974 and biomarkers.

- Efficacy: Overall response rate (ORR), complete response (CR) or partial

response (PR) rate and duration of response (DOR) defined according to RECIST.

Study description

Background summary

In vitro and in vivo studies show that LGK974 is a potent, selective inhibitor
of the Wnt pathway by blocking the activity of the protein porcupine. Porcupine

is a ubiquitously expressed protein on the cell membrane. It is involved in activation of the Wnt pathway, which is required for normal cellular proliferation and differentiation. Several lines of evidence suggest that Wnt pathway signaling may be important in breast cancer (lobular and triple negative), melanoma, pancreatic adenocarcinoma and perhaps other cancers. Inhibition of the Wnt pathway by blocking the activity of porcupine could therefore be associated with anti-tumor activity in these patients.
PDR001 is an anti-PD-1 antilichaam which blocks the binding of PD-L1 and PD-L2 to PD-1. PDR001 is cynomolgus cross-reactive and shows functional activity in vitro and ex vivo. Emerging data demonstrate a correlation between the presence of PD-L1 surface expression on tumor cells and tumor infiltrating immune cells and clinical efficacy of checkpoint inhibitors (anti-PD-1/PD-L1 therapies). Similarly, the presence of pre-existing exhausted tumor infiltrating lymphocytes (TIL) is associated with response to anti PD-L1/PD-1 treatment whilst immunological ignorance is associated with absence of clinical response.

Study objective

Primair:
Determine the MTD and/or recommended dose for expansion (RDE) of LGK974 as a single agent and
in combination with PDR001 when administered to adult patients with malignancies dependent on Wnt
ligands as specified in the inclusion criteria

Secundair:
Characterize the safety and tolerability of LGK974 single agent and in combination with PDR001
Evaluate the single dose and multiple dose PK of LGK974 and its pharmacologically active metabolite,
LHA333 in single agent dosing, and PK of LGK974 in combination with PDR001
Assess the PD response to LGK974 in tumor tissue and/or skin
Establish the PK/PD relationship of LGK974
Assess the anti-tumor activity of LGK974 as a single agent and in combination with PDR001

Study design

This open-label, multicenter, phase 1 study will be the first to administer LGK974 single and in combination with PDR001 in humans.

LGK974 single:
The study starts with a dose escalation part, in which patients will daily take one or more capsules of LGK974. The treatment consists of cylces of 28 days. Groups of patients will receive a dose, which will be step-wise increased for each group, to determine the MTD (maximum tolerated dose). The start dose is 10

mg per day. A two-parameter Bayesian logistic regression model will be used to determine the MTD. It is anticipated that approximately 80 patients will be treated in the dose escalation part of the study. When the MTD is established, the patient group will be expanded (dose expansion phase of the study) with at approximately 30 patients, for further evaluation of the safety and tolerability, and to make a preliminary assessment of the efficacy of this dose of LGK974.
Of these 30 patients in the expansion phase approximately 10 patients in each of the following 3 specific populations:
* - documented B-RAF mutant colorectal cancer with RNF43 mutation and/or RSPO fusion
* - pancreatic adenocarcinoma with RNF43 mutation.
- tumors of any histological origin with documented genetic alterations upstream in the Wnt
signaling pathway, such as gene fusions in RSPO and mutations in RNF43 (with prior
agreement with Novartis).

Combination of LGK974 and PDR001:
same as single. Additionally PDR001 will be given ones in the 28 days by infuse.
35 patients will be enrolled for the escalation part (patients with melanoma that was previously primary refractory to anti-PD-1 therapy) and 40 patients will be enrolled for the expansion part (pancreatic cancer, triple negative breast cancer (TNBC), melanoma and head and neck squamous cell cancer).

Patients will be treated until disease progression or unacceptable toxicity occurs. Patients could discontinue the study by withdrawal of consent or treatment could be discontinued at the discretion of the investigator when it is no longer in the best interest of the patient.

Intervention

Daily intake of one or more capsules of LGK974 (alternative dosing schedules are possible).
PDR001 will be administered via i.v. infusion over 30 minutes once evey 4 weekson day 1 of east cycle.

Study burden and risks

LGK974 has not yet been given to humans. Based on the results of animal studies the most likely and most severe side effects of LGK974 in humans are expected to be in the intestines and include effects such as diarrhea, abdominal discomfort, infection, and bleeding. The effects on the bone marrow may cause reduction in the number of blood cells in the body. This can result in fatigue, infection and bleeding. The effects on the kidneys and liver might cause these

organs to not function properly. The effects seen in animals on growing teeth and bones are not expected to be seen in adults, but LGK974 may prevent normal healing of bone fractures and the possibility of tooth problems cannot be excluded.

Risks that were seen recently with PDR001 include: diarrhea, fatique, nausea, pruritus, hypotheyroidism, rash and vomiting. As a PD-1 class of drugs also could cause immune-related toxicities including skin reactions and pneumonitis. The most common risks supected of LGK974 include: dysgeusia, decresed appetite, nausea fatique, diarhea, vomiting, hypercalcemia and hypomagnesemia.

Other risks and inconveniences could occur due to blood sampling and collection of skin or tumor samples. Patiënts will be exposed to radiation when undergoing a CT, DEXA scan and X ray. The radiation exposure will not exceed the maximum ranges that are set within the Netherlands. An allergic reaction to the contrast used for CT scan could occur.

Contacts

Public
Novartis

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Amsterdam 1101 BX
NL
Scientific
Novartis

Haaksbergweg 16
Amsterdam 1101 BX
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Diagnosis of locally advanced or metastatic cancer that has progressed despite standard therapy or for which no effective standard therapy exists and histological confirmation of one of the following diseases indicated below:
• Single agent LGK974- Dose escalation part: documented B-RAF mutant colorectal cancer; or pancreatic adenocarcinoma. In addition, tumors of any histological origin with previously documented genetic alterations upstream in the Wnt signaling pathway, such as gene fusions in RSPOs and mutations in RNF43, are eligible with prior agreement with Novartis
• Single Agent LGK974 -Dose expansion part: documented B-RAF mutant colorectal cancer with documented RNF43 mutation and/or RSPO fusion of pancreatic adenocarcinoma with documented RNF43 mutation. In addition, patients with tumors of any histological origin with documented genetic alterations upstream in the Wnt signaling pathway, such as gene fusions in RSPOs and mutations in RNF43, are eligible with prior agreement with Novartis• LGK974 with PDR001: Dose escalation: patients with the following cancers that were previously treated with anti-PD-1 therapy and whose best response on that therapy was progressive disease (i.e., primary refractory): melanoma, lung SCC, HNSCC. Patients with esophageal SCC, cervical SCC or TNBC who are either naive or primary refractory to prior anti-PD-1 therapy.
• LGK974 with PDR001: Dose expansion: patients with pancreatic cancer, or TNBC, or melanoma, or head and neck squamous cell cancer.
• Patients with cancers of squamous cell histology must have had progression on or after, or intolerance to, a prior platinum-containing chemotherapy regimen-
WHO performance status of 0-2
eker(s)

Exclusion criteria

1.Patients with a primary central nervous system tumor or with uncontrolled, symptomatic brain metastases that have not been adequately treated. Patients with symptomatic brain metastases that have been adequeatly treated, such as with radiotherapy or resection, are not excluded if any associated symptoms are stable, and do not require ongoing glucocorticoid therapy.
2: Impaired cardiac function including any one of the following:
- Corrected QT interval (QTc) > 480 milliseconds on baseline ECG.
- Clinically significant, uncontrolled heart disease (e.g. unstable angina,

congestive heart failure, uncontrolled hypertention, ventricular or atrial arrhythmias)
- Myocardial infarction (MI) within the prior 3 months.
3.Patients with any of the following laboratory values at baseline:
- Absolute neutrophil count (ANC) < 1.0 109/L
- Platelets < 75 109/L
- Hemoglobin < 9.0 g/dL
- Calculated or measured creatinine clearance (using Cockcroft-Gault formula) < 50 ml/min
- Bilirubin > 1.5 x ULN
- Aspartate transaminase (AST) and alanine transaminase (ALT) > 3.0 x ULN, except for patients with liver metastasis who are excluded if AST and ALT > 5.0 x ULN.
4. Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of oral LGK974 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).
5. Presence of >CTCAE Grade 2 toxicity (except alopecia) due to prior therapy.
6.Malignant disease other than that being treated in this study.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-12-2011
Enrollment:	33
Type:	Actual

Ethics review

Approved WMO

Date:	01-08-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-11-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-10-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-10-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-12-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-02-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-02-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-02-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	08-07-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-07-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-05-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-06-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-10-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-11-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-01-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-02-2015

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-09-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-10-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-04-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	27-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Application type:	Amendment
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Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-06-2018
Application type:	Amendment

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Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Application type:	Amendment
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Approved WMO Date:	21-11-2018
Application type:	Amendment
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Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Date:	20-05-2019
Application type:	Amendment
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Application type:	Amendment
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Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-000495-33-NL
ClinicalTrials.gov	NCT01351103
CCMO	NL37140.078.11